

### REMARKS

Favorable reconsideration and allowance of the claims of the present, as amended herein, application are respectfully requested.

Applicants have requested the requisite certified copy of EP 02078164.7 and will provide same as soon as it is received.

In the present Office Action, Claim 7 stands rejected under 35 U.S.C. §112, second paragraph. Specifically, the Examiner alleges that Claim 7 provides for the use of compounds of formula (I), but it does not set forth any steps involved in the method/process. Moreover, Claim 7 stands rejected under 35 U.S.C. §101 as allegedly lacking proper definition of a process claimed thereof for the same reason as explained above.

In response, applicants have deleted Claim 7 without prejudice. It is to be noted that applicants reserve the right to file a continuation application to cover the deleted subject matter.

Furthermore, Claims 1-4 stand rejected under 35 USC §102(b) as allegedly anticipated by US Patent No. 5,834,504 to Tang et al. Specifically, the Examiner alleges that Tang et al. teaches a compound of 3-[(2,4-Dimethylpyrrol-5-yl)methylene]-2-indolinone as well as the method of making the same (see Column 22, lines 42-49). Although the present invention claims an isotopically labeled carbonium 14 [ $^{14}\text{C}$ ] on the methylene carbon of said compound, the Examiner avers that  $^{14}\text{C}$  is within the "natural abundance" of carbon atoms and therefore the isotopically labeled compound claimed in the present invention is inherently present in the cited reference. As such, the Examiner is of the opinion that Claims 1-4 are anticipated by the teachings of the cited reference.

In response, applicants submit that the claims of the present application are not anticipated by Tang et al. for the reasons as set forth below.

Concerning the §102(b) rejection, it is axiomatic that anticipation under §102 requires that the prior art reference disclose each and every element of the claim to which it is applied. In re King, 801 F.2d, 1324, 1326, 231 USPQ 136, 138 (Fed. Cir. 1986). Thus, there must be no differences between the subject matter of the claim and the description of the claimed subject matter in the disclosure of the prior art reference. Id. Stated another way, the reference must contain within its four corners a description of the invention, as claimed. Id. The corollary of the rule is equally applicable: Absence from the applied reference of any claimed element negates anticipation. Kloster Speedsteel AB v. Crucible Inc., 793 F.2d 1565, 1571, 230 USPQ 81, 84 (Fed. Cir. 1986).

Applicants submit that the claims of the present application are not anticipated by the disclosure of the Tang et al. since the applied reference does not disclose: (a) indolylidene-methyl-pyrroles compounds being [<sup>14</sup>C] isotopically labeled at the methyldene moiety; (b) such indolylidene-methyl-pyrroles compounds have a high degree of radiochemical purity, i.e., the compound of 3-[(2,4-Dimethylpyrrol-5-yl) [<sup>14</sup>C] methylene]-2-indolinone is 99% radiochemically pure, see Page 10, lines 14-15; and (c) the process of making said compounds by reacting an [<sup>14</sup>C] isotopically labeled 2-carboxaldehyde pyrrole with an oxindole. Instead, the teachings from Tang et al. provide: (a) a compound of 3-[(2,4-Dimethylpyrrol-5-yl)methylene]-2-indolinone which is not isotopically labeled; (b) such compound is not radiochemically pure since it is a mixture of [<sup>12</sup>C] and [<sup>13</sup>C]; and (c) a process of making said compound by reacting an non-isotopically labeled 2-carboxaldehyde pyrrole derivative with an oxindole.

Applicants further submit that although Tang et al. may disclose the compound of 3-[(2,4-Dimethylpyrrol-5-yl)methylene]-2-indolinone, such compound is a mixture of [ $^{12}\text{C}$ ] and [ $^{13}\text{C}$ ] at the methyldene moiety since [ $^{12}\text{C}$ ] and [ $^{13}\text{C}$ ], rather than [ $^{14}\text{C}$ ], are the “natural abundance” of the carbon atom. For the convenience of the Examiner, applicants enclose herewith a copy of the table of atomic masses and abundancies from the Handbook of Chemistry and Physics. Said table shows that [ $^{12}\text{C}$ ] has an abundance of 98.93% and [ $^{13}\text{C}$ ] has an abundance of 1.07%. Since [ $^{14}\text{C}$ ] is not a naturally abundant carbon atom, it follows that a compound isotopically labeled with [ $^{14}\text{C}$ ] is not inherent from the same compound without being isotopically labeled with [ $^{14}\text{C}$ ]. Moreover, the compounds claimed in the present invention have a high degree of radiochemical purity with respect to [ $^{14}\text{C}$ ] whereas the compound disclosed from Tang et al. is a mixture of [ $^{12}\text{C}$ ] and [ $^{13}\text{C}$ ]. It is stressed that compounds having a high level of [ $^{14}\text{C}$ ] radiochemical purity have different physical and chemical properties from compounds which are a mixture of [ $^{12}\text{C}$ ] and [ $^{13}\text{C}$ ]. As such, compounds claimed in the present invention are fundamentally distinct from the compound of 3-[(2,4-Dimethylpyrrol-5-yl)methylene]-2-indolinone disclosed from Tang et al.

Inasmuch as Tang et al. does not teach or suggest the claimed compounds of the present invention, Tang et al. also fails to teach or suggest the method of preparation of the claimed compounds of the present invention.

The foregoing remarks clearly demonstrate that Tang et al. does not teach each and every aspect of the claimed invention, as required by King and Kloster Speedsteel; therefore the claims of the present application are not anticipated by the disclosure of Tang et al. Applicants respectfully submit that the instant §102 rejection over Tang et al. has been obviated, and withdrawal thereof is respectfully requested.

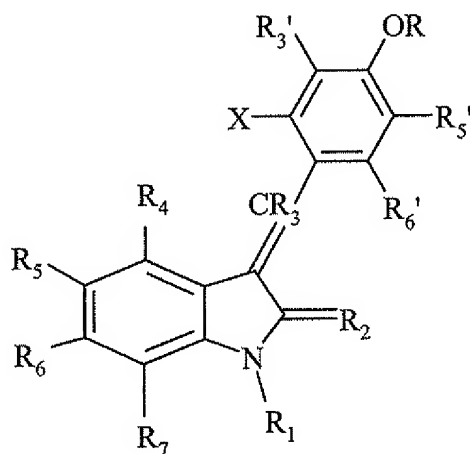
In the Office Action, Claims 1-5 and 7 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Tang et al. in view of Plieninger et al. Specifically, the Examiner avers that Tang et al. teach a compound of 3-[(2,4-Dimethylpyrrol-5-yl)methylene]-2-indolinone as well as the method of making same by reacting the oxindole with optionally substituted 2-carboxaldehyde pyrrole in piperidine. The Examiner also concedes that Tang et al. does not teach that [ $^{14}\text{C}$ ] is present in the methylene group in more than the natural abundance, nor that the synthesis is done in pyrrolidine, or the use of the compound for absorption, distribution, metabolism and excretion studies. The Examiner further alleges that Plieninger et al. teaches a substituted 2-carboxaldehyde pyrrole wherein [ $^{14}\text{C}$ ] is present in the carbon of the aldehyde group. Therefore, the Examiner asserts that a person skilled in the art would be motivated to react the substituted 2-carboxaldehyde pyrrole with the oxindole in pyrrolidine to make the claimed compound of the present invention, since one skilled in the art routinely uses radioisotopes for studies within the body for absorption, distribution, metabolism, and excretion studies, and radiolabelled compounds can be easily analyzed by mass spectroscopy.

In response, applicants submit that the claims of the present application are not rendered obvious by the disclosures of Tang et al. in view of Plieninger et al., since the cited two references, either alone or in combination, do not teach, disclose or suggest the claimed invention.

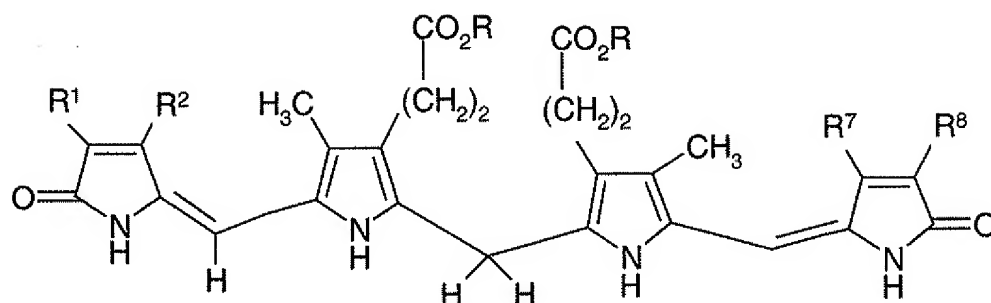
With respect to Tang et al., the primary reference, applicants submit that there are several differences between the compounds and the process of making such compounds in Tang et al. and that of the present invention as clearly stated above. Thus, the present invention is not obvious to one of ordinary skill in the art from the teaching of Tang et al.

In view of the above remarks, applicants submit that it is not obvious for a person skilled in the art to select a [ $^{14}\text{C}$ ] isotopically labeled 2-carboxaldehyde pyrrole derivative, react it with an oxindole under a modified base, i.e., pyrrolidine, to obtain a compound of 3-[(2,4-Dimethylpyrrol-5-yl) [ $^{14}\text{C}$ ]methylene]-2-indolinone with high radiochemical purity wherein such compound can be used for absorption, distribution, metabolism and excretion studies.

With respect to the secondary reference, Plieninger et al. teaches the use of a compound of substituted 2-carboxaldehyde pyrrole wherein [ $^{14}\text{C}$ ] is present in the carbon of the aldehyde group, as an intermediate in obtaining a final compound with the structure set out below. Applicants submit that there would be no reason for a person skilled in the art to combine the primary and secondary references in the first instance since the cited references relate to different classes of compounds and different applications, for example, the primary reference is directed to 3-(2'-halobenzylidenyl)-2-indolinone compounds (structure shown below) in the treatment of abnormal cell proliferation, whereas the secondary reference relates to a process of making a mixture of bilirubin-IX $\alpha$ -dimethyl ester and bilirubin-XIII $\alpha$ -dimethyl ester.



Compound taught by Tang et al.



Compound taught by Plieninger et al.

Moreover, even when combined, the secondary reference together with the primary reference does not overcome the deficiencies of the primary reference, since Plieninger et al. do not teach, disclose or suggest a compound of 3-[(2,4-Dimethylpyrrol-5-yl) [<sup>14</sup>C]methylene]-2-indolinone with high [<sup>14</sup>C] radiochemical purity. Inasmuch as neither Tang et al. nor Plieninger et al individually teach, disclose or suggest a compound of 3-[(2,4-Dimethylpyrrol-5-yl) [<sup>14</sup>C]methylene]-2-indolinone with high [<sup>14</sup>C] radiochemically purity, the combination cannot teach, disclose or suggest said compound.

In view of the above remarks, applicants submit that the present invention is not obvious over Tang et al. in view of Plieninger et al. Applicants respectfully submit that the instant §103 rejection over Tang et al. in view of Plieninger et al. has been obviated, and withdrawal thereof is respectfully requested.

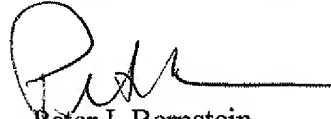
In the Office Action, Claim 6 stands rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Plieninger et al. Specifically, the Examiner alleges that Plieninger et al. does not teach a methyl group in the 5-position of the pyrrolidine, but a person skilled in the art would be motivated to modify the structure and arrive to the present invention.

In response, applicants submit that the compounds recited in Claim 6 are not disclosed or suggested by Plieninger et al. Moreover, a person skilled in the art would not be motivated to modify the structure with a reasonable expectation of success. Therefore,

applicants respectfully submit that the instant §103 rejection over Plieninger et al. has been obviated, and withdrawal thereof is respectfully requested.

Thus, in view of the foregoing amendments and remarks, it is firmly believed that the present case is in condition for allowance, which action is earnestly solicited.

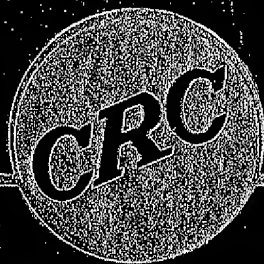
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# ATOMIC MASSES AND ABUNDANCES

This table lists the mass (in atomic mass units, symbol u) and the natural abundance (in percent) of the stable nuclides and a few important radioactive nuclides. A complete table of all nuclides may be found in Section 11 ("Table of the Isotopes").

The atomic masses were taken from the 2003 evaluation of Audi, Wapstra, and Thibault (References 2, 3). The number in parentheses following the mass value is the uncertainty in the last digit(s) given. An asterisk \* after an entry indicates the mass value was derived not purely from experimental data, but at least partly from systematic trends.

Natural abundance values were taken from the IUPAC Technical Report "Atomic Weight of the Elements: Review 2000" (Reference 4); these entries are also followed by uncertainties in the last digit(s) of the stated values. This uncertainty includes both the estimated measurement uncertainty and the reported range of variation in different terrestrial sources of the element (see Reference 4 for full

details and caveats regarding elements whose abundance is variable). The absence of an entry in the Abundance column indicates a radioactive nuclide not present in nature or an element whose isotopic composition varies so widely that a meaningful natural abundance cannot be defined.

## References

1. Holden, N. E., "Table of the Isotopes", in Lide, D. R., Ed., *CRC Handbook of Chemistry and Physics*, 86th Ed., CRC Press, Boca Raton FL, 2005.
2. Audi, G., Wapstra, A. H., and Thibault, *Nucl. Phys.*, A729, 336, 2003.
3. Audi, G., and Wapstra, A. H., Atomic Mass Data Center, World Wide Web site, <<http://www.nndc.bnl.gov/amdc/index.html>>
4. de Laeter, J. R., Böhlke, J. K., De Bièvre, P., Hidaka, H., Peiser, H. S., Rosman, K. J. R., and Taylor, P. D. P., *Pure Appl. Chem.* 75, 683, 2003.

Z	Isotope	Mass in u	Abundance in %
1	<sup>1</sup> H	1.00782503207(10)	99.9885(70)
	<sup>2</sup> H	2.0141017778(4)	0.0115(70)
	<sup>3</sup> H	3.0160492777(25)	
2	<sup>3</sup> He	3.0160293191(26)	0.000134(3)
	<sup>4</sup> He	4.00260325415(6)	99.999866(3)
3	<sup>6</sup> Li	6.015122795(16)	7.59(4)
	<sup>7</sup> Li	7.01600455(8)	92.41(4)
4	<sup>9</sup> Be	9.0121822(4)	100
5	<sup>10</sup> B	10.0129370(4)	19.9(7)
	<sup>11</sup> B	11.0093054(4)	80.1(7)
6	<sup>12</sup> C	11.0114336(10)	
	<sup>13</sup> C	12.0000000(0)	98.93(8)
	<sup>14</sup> C	13.0033548378(10)	1.07(8)
	<sup>15</sup> C	14.003241989(4)	
7	<sup>14</sup> N	14.0030740048(6)	99.636(7)
	<sup>15</sup> N	15.0001088982(7)	0.364(7)
8	<sup>16</sup> O	15.99491461956(16)	99.757(16)
	<sup>17</sup> O	16.99913170(12)	0.038(1)
	<sup>18</sup> O	17.9991610(7)	0.205(14)
9	<sup>19</sup> F	18.0009380(6)	
	<sup>20</sup> F	18.99840322(7)	100
10	<sup>20</sup> Ne	19.9924401754(19)	90.48(3)
	<sup>21</sup> Ne	20.99384668(4)	0.27(1)
	<sup>22</sup> Ne	21.991385114(19)	9.25(3)
11	<sup>23</sup> Na	21.9944364(4)	
	<sup>24</sup> Na	22.9897692809(29)	100
	<sup>25</sup> Na	23.99096278(8)	
12	<sup>24</sup> Mg	23.985041700(14)	78.99(4)
	<sup>25</sup> Mg	24.98583692(3)	10.00(1)
	<sup>26</sup> Mg	25.982592929(30)	11.01(3)
13	<sup>27</sup> Al	26.98153863(12)	100
14	<sup>28</sup> Si	27.9769265325(19)	92.223(19)
	<sup>29</sup> Si	28.976494700(22)	4.685(8)
	<sup>30</sup> Si	29.97377017(3)	3.092(11)
15	<sup>31</sup> P	30.97376163(20)	100
	<sup>32</sup> P	31.97390727(20)	
16	<sup>32</sup> S	31.97207100(15)	94.99(26)
	<sup>33</sup> S	32.97145876(15)	0.75(2)
	<sup>34</sup> S	33.96786690(12)	4.25(24)
	<sup>35</sup> S	34.96903216(11)	
	<sup>36</sup> S	35.96708076(20)	0.01(1)

Z	Isotope	Mass in u	Abundance in %
17	<sup>35</sup> Cl	34.96885268(4)	75.76(10)
	<sup>37</sup> Cl	36.96590259(5)	24.24(10)
18	<sup>36</sup> Ar	35.967545106(29)	0.3365(30)
	<sup>38</sup> Ar	37.9627324(4)	0.0632(5)
	<sup>40</sup> Ar	39.9623831225(29)	99.6003(30)
19	<sup>39</sup> K	38.96370668(20)	93.2581(44)
	<sup>40</sup> K	39.96399848(21)	0.0117(1)
	<sup>41</sup> K	40.96182576(21)	6.7302(44)
	<sup>42</sup> K	41.96240281(24)	
	<sup>43</sup> K	42.960716(10)	
20	<sup>40</sup> Ca	39.96259098(22)	96.941(156)
	<sup>42</sup> Ca	41.95861801(27)	0.647(23)
	<sup>43</sup> Ca	42.9587666(3)	0.135(10)
	<sup>44</sup> Ca	43.9554818(4)	2.086(110)
	<sup>45</sup> Ca	44.9561866(4)	
	<sup>46</sup> Ca	45.9536926(24)	0.004(3)
	<sup>47</sup> Ca	46.9545460(24)	
	<sup>48</sup> Ca	47.952534(4)	0.187(21)
21	<sup>45</sup> Sc	44.9559119(9)	100
22	<sup>46</sup> Ti	45.9526316(9)	8.25(3)
	<sup>47</sup> Ti	46.9517631(9)	7.44(2)
	<sup>48</sup> Ti	47.9479463(9)	73.72(3)
	<sup>49</sup> Ti	48.9478700(9)	5.41(2)
	<sup>50</sup> Ti	49.9447912(9)	5.18(2)
23	<sup>50</sup> V	49.9471585(11)	0.250(4)
	<sup>51</sup> V	50.9439595(11)	99.750(4)
24	<sup>50</sup> Cr	49.9460442(11)	4.345(13)
	<sup>51</sup> Cr	50.9447674(11)	
	<sup>52</sup> Cr	51.9405075(8)	83.789(18)
	<sup>53</sup> Cr	52.9406494(8)	9.501(17)
	<sup>54</sup> Cr	53.938804(8)	2.365(7)
25	<sup>54</sup> Mn	53.9403589(14)	
	<sup>55</sup> Mn	54.9380451(7)	100
26	<sup>52</sup> Fe	51.948114(7)	
	<sup>54</sup> Fe	53.9396105(7)	5.845(35)
	<sup>56</sup> Fe	54.9382934(7)	
	<sup>57</sup> Fe	55.9349375(7)	91.754(36)
	<sup>58</sup> Fe	56.9353940(7)	2.119(10)
	<sup>59</sup> Fe	57.9332756(8)	0.282(4)
	<sup>60</sup> Fe	58.9348755(8)	
27	<sup>57</sup> Co	56.9362914(8)	